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Gene Section
Review

PCSK6 (proprotein convertase subtilisin/kexin type 6)

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Abstract

Review on PCSK6, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: PACE4, SPC4

HGNC (Hugo): PCSK6

Location: 15q26.3

DNA/RNA

Description

This gene can be found on chromosome 15 at location: 101844134-102029873.

Transcription

The DNA sequence contains 23 exons and the transcript length: 4236 bps translated to a 968 residues protein.

Protein

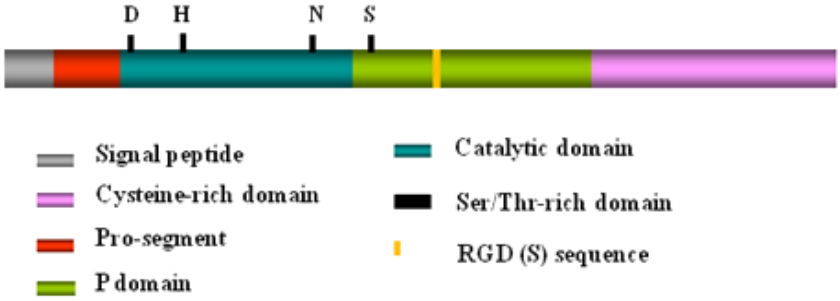
Description

PCSK6 is a member of the family of subtilisin-like proprotein convertases (PCs) that process precursor proteins at their paired basic amino acid processing sites (RXR).

This protease undergoes an initial autocatalytic processing event in the endoplasmic reticulum (ER) to generate a heterodimer which exits the ER and sorts to the trans-Golgi network (TGN). In the TGN a second autocatalytic cleavage takes place in order to release an active PCSK6.

Expression

PCSK6 is expressed in many tissues and encoded by different alternatively spliced mRNAs: the PACE4A-I form is secreted and expressed in heart, brain, placenta, lung, skeletal muscle, kidney, pancreas, but at comparatively higher levels in the liver. Isoform PACE4A-II is secreted and at least expressed in placenta. Isoform PACE4B is secreted and was only found in the embryonic kidney cell line from which it was isolated. Isoforms PACE4C and PACE4D are located in ER (not secreted, remain probably inactive unprocessed form in endoplasmic reticulum) and expressed in placenta too. Isoforms PACE4E-I and PACE4E-II are probably retained intracellularly through a hydrophobic cluster in their C-terminus, and expressed in cerebellum (E-I and -II), placenta and pituitary (only E-I). The PACE4CS was also found to probably lack enzymatic activity.



Localisation

PCSK6 is activated predominantly at the cell surface and able to process its substrates within the extracellular matrix and cell surface.

Function

PCSK6 induce protein precursors cleavage at the R-X-(K/R)-R motif to release mature proteins. PCSK6 substrates include enzymes (ADAMTS-4 and ADAMTS-5), HIV accessory protein Vpr, NODAL, TGF-beta related proteins, proalbumin and von Willebrand factor. This protein is thought to play a role in tumor progression and left-right patterning.

Homology

The PCSK6 catalytic domain has a high percentage of homology with those of the other PCs: 42% between PCSK6 and Furin.

Implicated in

Breast cancer

Higher expression of PCSK6 has been detected in human breast cancer. There was a correlation between the amount of PACE4 gene product and estrogen receptor content.

Prostate cancer

A recent study demonstrated that PSCK6 was highly overexpressed in prostate cancer tissues.

Skin cancer

Transgenic expression of PACE4 in keratinocytes of the epidermal basal layer was more susceptible to chemical carcinogenesis, evidenced by increased tumor multiplicity, tumor volume, and metastasis.

Association with degree of handedness

There is a significant association with a VNTR polymorphism in PCSK6 and handedness.

References

Akamatsu T, Azlina A, Purwanti N, Karabasil MR, Hasegawa T, Yao C, Hosoi K. Inhibition and transcriptional silencing of a subtilisin-like proprotein convertase, PACE4/SPC4, reduces the branching morphogenesis of and AQP5 expression in rat embryonic submandibular gland. Dev Biol. 2009 Jan 15;325(2):434-43

Arning L, Ocklenburg S, Schulz S, Ness V, Gerding WM, Hengstler JG, Falkenstein M, Epplen JT, Güntürkün O, Beste C. PCSK6 VNTR Polymorphism Is Associated with Degree of Handedness but Not Direction of Handedness. PLoS One. 2013;8(6):e67251

Artenstein AW, Opal SM. Proprotein convertases in health and disease. N Engl J Med. 2011 Dec 29;365(26):2507-18

Bassi DE, Cenna J, Zhang J, Cukierman E, Klein-Szanto AJ. Enhanced aggressiveness of benzopyrene-induced squamous carcinomas in transgenic mice overexpressing the proprotein convertase PACE4 (PCSK6). Mol Carcinog. 2015 Oct;54(10):1122-31

Bassi DE, Lopez De Cicco R, Cenna J, Litwin S, Cukierman E, Klein-Szanto AJ. PACE4 expression in mouse basal keratinocytes results in basement membrane disruption and acceleration of tumor progression. Cancer Res. 2005 Aug 15;65(16):7310-9

Bassi DE, Mahloogi H, Klein-Szanto AJ. The proprotein convertases furin and PACE4 play a significant role in tumor progression. Mol Carcinog. 2000 Jun;28(2):63-9

Bassi DE, Zhang J, Cenna J, Litwin S, Cukierman E, Klein-Szanto AJ. Proprotein convertase inhibition results in decreased skin cell proliferation, tumorigenesis, and metastasis. Neoplasia. 2010 Jul;12(7):516-26

Beck S, Le Good JA, Guzman M, Ben Haim N, Roy K, Beermann F, Constam DB. Extraembryonic proteases regulate Nodal signalling during gastrulation. Nat Cell Biol. 2002 Dec;4(12):981-5

Blanchet MH, Le Good JA, Mesnard D, Oorschot V, Baflast S, Minchiotti G, Klumperman J, Constam DB. Cripto recruits Furin and PACE4 and controls Nodal trafficking during proteolytic maturation. EMBO J. 2008 Oct 8;27(19):2580-91

Byun S, Tortorella MD, Malfait AM, Fok K, Frank EH, Grodzinsky AJ. Transport and equilibrium uptake of a peptide inhibitor of PACE4 into articular cartilage is dominated by electrostatic interactions. Arch Biochem Biophys. 2010 Jul;499(1-2):32-9

Couture F, D'Anjou F, Desjardins R, Boudreau F, Day R. Role of proprotein convertases in prostate cancer progression. Neoplasia. 2012 Nov;14(11):1032-42

Creemers JW, Khatib AM. Knock-out mouse models of proprotein convertases: unique functions or redundancy? Front Biosci. 2008 May 1;13:4960-71

Decroly E, Wouters S, Di Bello C, Lazure C, Ruysschaert JM, Seidah NG. Identification of the paired basic convertases implicated in HIV gp160 processing based on in vitro assays and expression in CD4(+) cell lines. J Biol Chem. 1996 Nov 29;271(48):30442-50

Delic S, Lottmann N, Jetschke K, Reifenberger G, Riemenschneider MJ. Identification and functional validation of CDH11, PCSK6 and SH3GL3 as novel glioma invasion-associated candidate genes. Neuropathol Appl Neurobiol. 2012 Apr;38(2):201-12

Demidyuk IV, Shubin AV, Gasanov EV, Kurinov AM, Demkin VV, Vinogradova TV, Zinovyeva MV, Sass AV, Zborovskaya IB, Kostrov SV. Alterations in gene expression of proprotein convertases in human lung cancer have a limited number of scenarios. PLoS One. 2013;8(2):e55752

Diaz FJ, Sugiura K, Eppig JJ. Regulation of Pcsk6 expression during the preantral to antral follicle transition in mice: opposing roles of FSH and oocytes. Biol Reprod. 2008 Jan;78(1):176-83

Fu J, Bassi DE, Zhang J, Li T, Cai KQ, Testa CL, Nicolas E, Klein-Szanto AJ. Enhanced UV-induced skin carcinogenesis in transgenic mice overexpressing proprotein convertases. Neoplasia. 2013 Feb;15(2):169-79

Fu Y, Nachtigal MW. Analysis of epigenetic alterations to proprotein convertase genes in disease. Methods Mol Biol. 2011;768:231-45

Inocencio NM, Sucic JF, Moehring JM, Spence MJ, Moehring TJ. Endoprotease activities other than furin and PACE4 with a role in processing of HIV-I gp160 glycoproteins in CHO-K1 cells. J Biol Chem. 1997 Jan 10;272(2):1344-8

Kang S, Zhao Y, Hu K, Xu C, Wang L, Liu J, Yao A, Zhang H, Cao F. miR-124 exhibits antiproliferative and antiaggressive effects on prostate cancer cells through PACE4 pathway. Prostate. 2014 Aug;74(11):1095-106

Khatib AM, Lahlil R, Scamuffa N, Akimenko MA, Ernest S, Lomri A, Lalou C, Seidah NG, Villoutreix BO, Calvo F, Siegfried G. Zebrafish ProVEGF-C expression, proteolytic processing and inhibitory effect of unprocessed ProVEGF-C during fin regeneration. PLoS One. 2010 Jul 2;5(7):e11438

Khatib AM, Siegfried G, Prat A, Luis J, Chrétien M, Metrakos P, Seidah NG. Inhibition of proprotein convertases is associated with loss of growth and tumorigenicity of HT-29 human colon carcinoma cells: importance of insulin-like growth factor-1 (IGF-1) receptor processing in IGF-1-mediated functions. J Biol Chem. 2001 Aug 17;276(33):30686-93

Koo BH, Kim HH, Park MY, Jeon OH, Kim DS. Membrane type-1 matrix metalloprotease-independent activation of pro-matrix metalloprotease-2 by proprotein convertases. FEBS J. 2009 Nov;276(21):6271-84

Kwiatkowska A, Couture F, Levesque C, Ly K, Desjardins R, Beauchemin S, Prahl A, Lammek B, Neugebauer W, Dory YL, Day R. Design, synthesis, and structure-activity relationship studies of a potent PACE4 inhibitor. J Med Chem. 2014 Jan 9;57(1):98-109

Lahlil R, Calvo F, Khatib AM. The potential anti-tumorigenic and anti-metastatic side of the proprotein convertases inhibitors. Recent Pat Anticancer Drug Discov. 2009 Jan;4(1):83-91

Lapierre M, Siegfried G, Scamuffa N, Bontemps Y, Calvo F, Seidah NG, Khatib AM. Opposing function of the proprotein convertases furin and PACE4 on breast cancer cells' malignant phenotypes: role of tissue inhibitors of metalloproteinase-1. Cancer Res. 2007 Oct 1;67(19):9030-4

Levesque C, Fugère M, Kwiatkowska A, Couture F, Desjardins R, Routhier S, Moussette P, Prahl A, Lammek B, Appel JR, Houghten RA, D'Anjou F, Dory YL, Neugebauer W, Day R. The Multi-Leu peptide inhibitor discriminates between PACE4 and furin and exhibits antiproliferative effects on prostate cancer cells. J Med Chem. 2012 Dec 13;55(23):10501-11

Lissitzky JC, Luis J, Munzer JS, Benjannet S, Parat F, Chrétien M, Marvaldi J, Seidah NG. Endoproteolytic processing of integrin pro-alpha subunits involves the redundant function of furin and proprotein convertase (PC) 5A, but not paired basic amino acid converting enzyme (PACE) 4, PC5B or PC7. Biochem J. 2000 Feb 15;346 Pt 1:133-8

Mahloogi H, Bassi DE, Klein-Szanto AJ. Malignant conversion of non-tumorigenic murine skin keratinocytes overexpressing PACE4. Carcinogenesis. 2002 Apr;23(4):565-72

Malfait AM, Seymour AB, Gao F, Tortorella MD, Le Graverand-Gastineau MP, Wood LS, Doherty M, Doherty S, Zhang W, Arden NK, Vaughn FL, Leaverton PE, Spector TD, Hart DJ, Maciewicz RA, Muir KR, Das R, Sorge RE, Sotocinal SG, Schorscher-Petcu A, Valdes AM, Mogil JS. A role for PACE4 in osteoarthritis pain: evidence from human genetic association and null mutant phenotype. Ann Rheum Dis. 2012 Jun;71(6):1042-8

Mesnard D, Donnison M, Fuerer C, Pfeffer PL, Constam DB. The microenvironment patterns the pluripotent mouse epiblast through paracrine Furin and Pace4 proteolytic activities. Genes Dev. 2011 Sep 1;25(17):1871-80

Mori K, Imamaki A, Nagata K, Yonetomi Y, Kiyokage-Yoshimoto R, Martin TJ, Gillespie MT, Nagahama M, Tsuji A, Matsuda Y. Subtilisin-like proprotein convertases, PACE4 and PC8, as well as furin, are endogenous proalbumin convertases in HepG2 cells. J Biochem. 1999 Mar;125(3):627-33

Mori K, Kii S, Tsuji A, Nagahama M, Imamaki A, Hayashi K, Akamatsu T, Nagamune H, Matsuda Y. A novel human PACE4 isoform, PACE4E is an active processing protease containing a hydrophobic cluster at the carboxy terminus. J Biochem. 1997 May;121(5):941-8

Moulard M, Chaloin L, Canarelli S, Mabrouk K, Darbon H. Retroviral envelope glycoprotein processing: structural investigation of the cleavage site. Biochemistry. 1998 Mar 31;37(13):4510-7

Moulard M, Decroly E. Maturation of HIV envelope glycoprotein precursors by cellular endoproteases. Biochim Biophys Acta. 2000 Nov 10;1469(3):121-32

Mujoomdar ML, Hogan LM, Parlow AF, Nachtigal MW. Pcsk6 mutant mice exhibit progressive loss of ovarian function, altered gene expression, and formation of ovarian pathology. Reproduction. 2011 Mar;141(3):343-55

Nagahama M, Taniguchi T, Hashimoto E, Imamaki A, Mori K, Tsuji A, Matsuda Y. Biosynthetic processing and quaternary interactions of proprotein convertase SPC4 (PACE4). FEBS Lett. 1998 Aug 28;434(1-2):155-9

Perisic L, Hedin E, Razuvaev A, Lengquist M, Osterholm C, Folkersen L, Gillgren P, Paulsson-Berne G, Ponten F, Odeberg J, Hedin U. Profiling of atherosclerotic lesions by gene and tissue microarrays reveals PCSK6 as a novel protease in unstable carotid atherosclerosis. Arterioscler Thromb Vasc Biol. 2013 Oct;33(10):2432-43

Scamuffa N, Basak A, Lalou C, Wargnier A, Marcinkiewicz J, Siegfried G, Chrétien M, Calvo F, Seidah NG, Khatib AM. Regulation of prohepcidin processing and activity by the subtilisin-like proprotein convertases Furin, PC5, PACE4 and PC7. Gut. 2008 Nov;57(11):1573-82

Scerri TS, Brandler WM, Paracchini S, Morris AP, Ring SM, Richardson AJ, Talcott JB, Stein J, Monaco AP. PCSK6 is associated with handedness in individuals with dyslexia. Hum Mol Genet. 2011 Feb 1;20(3):608-14

Seidah NG, Khatib AM, Prat A. The proprotein convertases and their implication in sterol and/or lipid metabolism. Biol Chem. 2006 Jul;387(7):871-7

Seidah NG, Prat A. The biology and therapeutic targeting of the proprotein convertases. Nat Rev Drug Discov. 2012 May;11(5):367-83

Seidah NG, Sadr MS, Chrétien M, Mbikay M. The multifaceted proprotein convertases: their unique, redundant, complementary, and opposite functions. J Biol Chem. 2013 Jul 26;288(30):21473-81

Seidah NG. What lies ahead for the proprotein convertases? Ann N Y Acad Sci. 2011 Mar;1220:149-61

Sfaxi F, Scamuffa N, Lalou C, Ma J, Metrakos P, Siegfried G, Ragg H, Bikfalvi A, Calvo F, Khatib AM. Repression of liver colorectal metastasis by the serpin Spn4A a naturally occurring inhibitor of the constitutive secretory proprotein convertases. Oncotarget. 2014 Jun 30;5(12):4195-210

Siegfried G, Basak A, Prichett-Pejic W, Scamuffa N, Ma L, Benjannet S, Veinot JP, Calvo F, Seidah N, Khatib AM. Regulation of the stepwise proteolytic cleavage and secretion of PDGF-B by the proprotein convertases. Oncogene. 2005 Oct 20;24(46):6925-35

Sucic JF, Moehring JM, Inocencio NM, Luchini JW, Moehring TJ. Endoprotease PACE4 is Ca2+-dependent and temperature-sensitive and can partly rescue the phenotype of a furin-deficient cell strain. Biochem J. 1999 May 1;339 (Pt 3):639-47

Taniguchi T, Kuroda R, Sakurai K, Nagahama M, Wada I, Tsuji A, Matsuda Y. A critical role for the carboxy terminal region of the proprotein convertase, PACE4A, in the regulation of its autocatalytic activation coupled with secretion. Biochem Biophys Res Commun. 2002 Jan 18;290(2):878-84

Tsuji A, Higashine K, Hine C, Mori K, Tamai Y, Nagamune H, Matsuda Y. Identification of novel cDNAs encoding human kexin-like protease, PACE4 isoforms. Biochem Biophys Res Commun. 1994 Apr 29;200(2):943-50

Tsuji A, Hine C, Tamai Y, Yonemoto K, Mori K, Yoshida S, Bando M, Sakai E, Mori K, Akamatsu T, Matsuda Y. Genomic organization and alternative splicing of human PACE4 (SPC4), kexin-like processing endoprotease. J Biochem. 1997 Aug;122(2):438-52

Tsuji A, Kanie H, Makise H, Yuasa K, Nagahama M, Matsuda Y. Engineering of alpha1-antitrypsin variants selective for subtilisin-like proprotein convertases PACE4 and PC6: importance of the P2' residue in stable complex formation of the serpin with proprotein convertase. Protein Eng Des Sel. 2007 Apr;20(4):163-70

Tsuji A, Sakurai K, Kiyokage E, Yamazaki T, Koide S, Toida K, Ishimura K, Matsuda Y. Secretory proprotein convertases PACE4 and PC6A are heparin-binding proteins which are localized in the extracellular matrix. Potential role of PACE4 in the activation of proproteins in the extracellular matrix. Biochim Biophys Acta. 2003 Jan 31;1645(1):95-104

Tsuji A, Yoshida S, Hasegawa S, Bando M, Yoshida I, Koide S, Mori K, Matsuda Y. Human subtilisin-like proprotein convertase, PACE4 (SPC4) gene expression is highly regulated through E-box elements in HepG2 and GH4C1 cells. J Biochem. 1999 Sep;126(3):494-502

Tsuji A. [Extracellular processing protease PACE4: significance of diversity of SPC family proteases]. Seikagaku. 2003 Apr;75(4):305-10

Viale A, Ortola C, Hervieu G, Furuta M, Barbero P, Steiner DF, Seidah NG, Nahon JL. Cellular localization and role of prohormone convertases in the processing of pro-melanin concentrating hormone in mammals. J Biol Chem. 1999 Mar 5;274(10):6536-45

Vollenweider F, Benjannet S, Decroly E, Savaria D, Lazure C, Thomas G, Chrétien M, Seidah NG. Comparative cellular processing of the human immunodeficiency virus (HIV-1) envelope glycoprotein gp160 by the mammalian subtilisin/kexin-like convertases. Biochem J. 1996 Mar 1;314 (Pt 2):521-32

Wang Y, Wang XH, Fan DX, Zhang Y, Li MQ, Wu HX, Jin LP. PCSK6 regulated by LH inhibits the apoptosis of human granulosa cells via activin A and TGFβ2. J Endocrinol. 2014 Jul;222(1):151-60

Yana I, Weiss SJ. Regulation of membrane type-1 matrix metalloproteinase activation by proprotein convertases. Mol Biol Cell. 2000 Jul;11(7):2387-401

Yoshida I, Koide S, Hasegawa SI, Nakagawara A, Tsuji A, Matsuda Y. Proprotein convertase PACE4 is down-regulated by the basic helix-loop-helix transcription factor hASH-1 and MASH-1. Biochem J. 2001 Dec 15;360(Pt 3):683-9

Yuasa K, Futamatsu G, Kawano T, Muroshita M, Kageyama Y, Taichi H, Ishikawa H, Nagahama M, Matsuda Y, Tsuji A. Subtilisin-like proprotein convertase paired basic amino acid-cleaving enzyme 4 is required for chondrogenic differentiation in ATDC5 cells. FEBS J. 2012 Nov;279(21):3997-4009

Yuasa K, Masuda T, Yoshikawa C, Nagahama M, Matsuda Y, Tsuji A. Subtilisin-like proprotein convertase PACE4 is required for skeletal muscle differentiation. J Biochem. 2009 Sep;146(3):407-15

Yuasa K, Suzue K, Nagahama M, Matsuda Y, Tsuji A. Transcriptional regulation of subtilisin-like proprotein convertase PACE4 by E2F: possible role of E2F-mediated upregulation of PACE4 in tumor progression. Gene. 2007 Nov 1;402(1-2):103-10

Zhong M, Benjannet S, Lazure C, Munzer S, Seidah NG. Functional analysis of human PACE4-A and PACE4-C isoforms: identification of a new PACE4-CS isoform. FEBS Lett. 1996 Oct 28;396(1):31-6

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